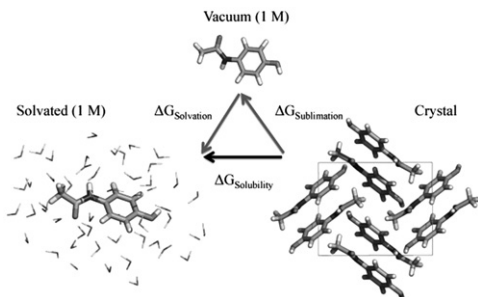


more rigorous physical model combined with effective sampling of molecular configurations is critical for binding affinity prediction to chemical accuracy, which is defined as within one order of magnitude of the true equilibrium dissociation constant. We have demonstrated that electrostatic interactions, especially electronic polarization, are critical for protein-ligand recognition due to the significant change in electrostatic environments between bulk water and protein pockets and have achieved encouraging success in treating charged species using the polarizable Atomic Multipole Optimized Energetics for Biomolecular Applications (AMOEBA) force field. To maintain *accuracy* while also achieving *efficiency*, AMOEBA has been combined with the Orthogonal Space Random Walk enhanced alchemical free energy algorithm. Here we present applications of this strategy for the computation of protein-ligand binding affinities and, for the first time, drug solubility from alchemical simulations using the Force Field X software.



2083-Plat

MloK1 Ligand Binding Simulations Indicate an Induced-Fit Mechanism

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Many ion channels such as the MloK1 channel are steered by ligand binding via conformational changes. Mainly two binding mechanisms have been proposed, induced fit and conformational selection. Using molecular dynamics simulations, we studied ligand binding of cyclic adenosine monophosphate at the cyclic nucleotide binding domain of the MloK1 ion channel of *Mesorizobium loti*. For this binding domain, both crystal and NMR structures have been determined for both the ligand free as well as for the ligand bound conformation.

In the simulations, spontaneous binding was observed, which enabled us to determine reaction coordinates for the ligand binding as well as for the associated conformational change of the protein. We used a combination of force probe simulations, umbrella sampling, and unbiased simulations to determine potentials of mean force along these reaction coordinates, transition rates, as well as free energy differences and barriers between the most relevant substates. Our results are compared with measured affinities and kinetics, and suggest an induced fit-mechanism.

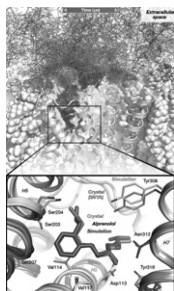
2084-Plat

Pathway and Mechanism of Drug Binding to G-Protein-Coupled Receptors

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How drugs bind to their receptors—from initial association, through entry into the binding pocket, to adoption of the final bound pose—has remained unknown, even for G-protein-coupled receptor modulators, which constitute one-third of all drugs. We captured this pharmaceutically critical process in atomic detail using the first unbiased molecular dynamics simulations in which drug molecules spontaneously associate with G-protein-coupled receptors to achieve final poses matching those determined crystallographically (PNAS 108:13118 (2011)). We found that several beta blockers and a beta agonist all traverse the same dominant pathway as they bind to the β_1 - and β_2 -adrenergic receptors, initially associating with a vestibule on each receptor's extracellular surface. Surprisingly, this association, at a distance of 15 Å from the binding pocket, often presents the largest energetic barrier to binding, despite the fact that subsequent entry into the pocket requires the receptor to deform and the drug to squeeze through a narrow passage. The early barrier may reflect the substantial dehydration that occurs as the drug associates with the vestibule. Our atomic-level description of the binding process suggests opportunities for allosteric modulation and provides a structural foundation for future optimization of binding and unbinding rates.



2085-Plat

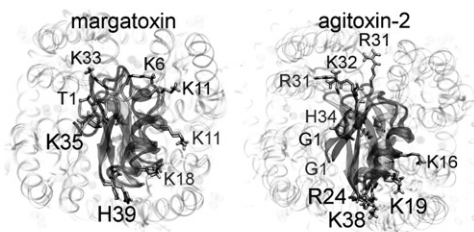
A General Prediction Method of Scorpion Toxins' Kv-Channel Selectivity Profiles using Haddock

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The active components of animal venoms are potentially useful in many electrophysiological and pharmacological applications due to their highly selective nature. Of this rich concoction, the binding mechanisms of many toxin types remain to be elucidated. We therefore present a preliminary method to deduce the selectivity profile of a peptide toxin against related channels by means of docking simulations. This is tested on the family of α -KTx scorpion toxins, for which structural and limited affinity data are available for over 20 toxins across seven sub-families. Docking simulations against Kv1.1, Kv1.2 and Kv1.3 were carried out under both blind-docking trials and common-lysine-motif trials, using the program HADDOCK.

This study reports on a selection of toxins for which validation can be best provided, given current limitations of docking accuracy. The general selectivity profiles of toxin-subfamilies can be deduced via consensus between closely related toxin-channel pairings. In particular, HADDOCK was able to classify α -KTX2 toxins as universal binders and α -KTX3 toxins as Kv1.3-selective binders. An estimation of individual selectivity profiles can be further deduced by program performance. This method is expected to be useful in the refinement of toxins for channel-subtype targeting.



2086-Plat

Design and Development of Drugs that Target Virus Ion Channels

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Virus ion channels are small (3-15 kD) peptides that aggregate to form ion channels that are important for viral infection¹. As viruses continue to pose a major worldwide health problem, these ion channels represent an exciting new target for therapeutic intervention. Viral ion channels that have been previously identified include Vpu of the human immunodeficiency virus (HIV) and P7 of Hepatitis C however it is the M2 influenza A protein that represents the best exploited ion channel drug target so far.

The proton-selective M2 ion channel is the target of the adamantane family of drug inhibitors. Use of the two most common adamantane inhibitors, amantadine and rimantadine have declined steadily over recent years due to the emergence of adamantane-resistant flu strains. We have conducted a series of surface plasmon resonance experiments designed to measure the affinity between several ion channel inhibitors and M22. By examining drug binding to a number of mutant M2 constructs (derived from adamantane-resistant strains), it was possible to establish the location of the drug binding sites and to rationalise the effect on drug binding of specific mutant residues. In light of these results, the prospect for future development of a new generation of M2 inhibitors will be discussed. Moreover, we explore the possibility of expanding this field of research to incorporate ion channel proteins from other viruses.

1. Gonzalez, M and Carrasco, L (2003). FEBS Lett. (2003) 552(1):28-34.

2. Rosenberg, M and Casarotto, M (2010) PNAS 107(31):13866-71.

2087-Plat

Kinome-Wide Spectroscopic Study of Drug Binding Site Electrostatics

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Small molecule kinase inhibitors have recently demonstrated dramatic potential for treating cancers caused by dysregulated protein kinases. The efficacy of these compounds is due to their ability to selectively target particular protein kinases, and this selectivity is remarkable given the fact that they bind to the ATP-binding site of the kinase domain, which is highly conserved in sequence across this large protein family. The origin of this selectivity is unknown, but must relate to differences in physical properties of the ATP-binding site among members of this protein family. The goal of this project is to assess how the evolutionary divergence of sequence and structure in the human kinome translates into variation in ATP-binding site electrostatics, and how this variation can be exploited to design highly selective inhibitors. I am using a clinically important class of kinase